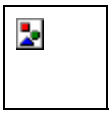

Department of Health and Human Services Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE
January 17, 2003
Michael Friedman
Executive Vice President and Chief Operating Officer
Purdue Pharma L.P.
The Purdue Frederick Company
One Stamford Forum
201 Tresser Boulevard
Stamford, CT 06901-3431
RE: NDA 20-553
OxyContin® (oxycodone HCI controlled-release) Tablets
MACMIS ID# 11400

WARNING LETTER

Dear Mr. Friedman:

This Warning Letter (revised) concerns the dissemination of promotional materials for the marketing of OxyContin® (oxycodone HCl controlled-release) Tablets by Purdue Pharma L.P. ("Purdue"). Specifically, we refer to two journal advertisements for OxyContin that recently appeared in the Journal of the American Medical Association (JAMA), one in the October 2, 2002 issue (A7038) (the "October Ad") and one in the November 13, 2002 issue (A7087) (the "November Ad"). The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these advertisements and has concluded that they are in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 331(a) and (b), 352 (n), and its implementing regulations.

Your journal advertisements omit and minimize the serious safety risks associated with OxyContin, and promote it for uses beyond which have been proven safe and effective. Specifically, your journal advertisements fail to present in the body of the advertisements any information from the boxed warning in the approved product labeling (PI) for OxyContin regarding the potentially fatal risks associated with the use of OxyContin and the abuse liability of OxyContin, which is a Schedule II controlled substance, and make unsubstantiated efficacy claims promoting the use of OxyContin for pain relief. Your journal advertisements also understate the minimal safety information that is presented.

Your advertisements thus grossly overstate the safety profile of OxyContin by not referring in the body of the advertisements to serious, potentially fatal risks associated with OxyContin, thereby potentially leading to prescribing of the product based on inadequate consideration of risk. In addition, your journal advertisements fail to present in the body of the advertisements critical information regarding limitations on the indicated use of OxyContin, thereby promoting

OxyContin for a much broader range of patients with pain than are appropriate for the drug. The combination in these advertisements of suggesting such a broad use of this drug to treat pain without disclosing the potential for abuse with the drug and the serious, potentially fatal risks associated with its use, is especially egregious and alarming in its potential impact on the public health.

Background

OxyContin was approved on December 12, 1995. Because the drug has a potential for abuse and has risks associated with its use that are serious and potentially fatal, the current PI for OxyContin contains a boxed warning that includes the following important information (emphasis in original):

- OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.
- Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
- OxyContin 80mg and 160mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.
- OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAXING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE

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Because of safety concerns, there are important limitations on the indicated use of OxyContin. The boxed warning contains the following bolded statements:

- OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.
- OxyContin Tablets are NOT intended for use as a pm analgesic.

The Precautions section of the OxyContin PI contains further bolded limitations on the appropriate use of OxyContin, namely:

- OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).
- OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.
- OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.

- OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

Moreover, because of the serious risks associated with OxyContin, it is contraindicated in a number of patient populations, including:

- Patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment)
- Patients with acute or severe bronchial asthma or hypercarbia
- Any patient who has or is suspected of having paralytic ileus.

Lack of Important Risk Information

Promotional materials are misleading if they fail to reveal material facts relating to potential consequences that may result from the use of the drug as recommended or suggested by the materials. Promotional materials are also misleading if they fail to include a balanced presentation of information relating to contraindications, warnings, precautions, and side effects associated with the use of a drug along with the presentation of promotional claims relating to the effectiveness and safety of the drug. Your journal advertisements are misleading because they make prominent claims of effectiveness for pain relief, but omit from the body of the advertisements crucial facts related to the serious, potentially fatal safety risks associated with the use of OxyContin, the potential for OxyContin to be abused, and the limitations on its appropriate indicated use.

Omission of material facts related to abuse liability and fatal risks
Specifically, your November Ad contains a two-page spread picturing a man fishing with a boy and featuring the prominent headline "THERE CAN BE LIFE WITH RELIEF." The words "LIFE WITH RELIEF" are the largest in the advertisement. The ad also features a graphic of two paper medication dosage cups with "8 AM" and "8 PM" next to them. The logo for OxyContin is right below, with the prominent tagline "IT WORKS." Your October Ad promotes "WHEN IT'S TIME TO CONSIDER Q4-6H OPIOIDS.. .REMEMBER, EFFECTIVE RELIEF TAKES JUST TWO." The claim "REMEMBER, EFFECTIVE RELIEF TAKES JUST TWO" is prominently highlighted in the middle of the ad, surrounded by comparative graphics of dosage cups which show only two dosage cups for OxyContin, as compared to six dosage cups for the other drugs. As with the November Ad, the logo for OxyContin is directly under the graphic of the two dosage cups, with the prominent tagline "IT WORKS." Therefore, the principal message of both advertisements appears to be that OxyContin offers effective pain relief and has convenient dosing.

These ad presentations, however, fail to present in the body of the advertisements critical safety information related to the use of OxyContin needed to balance these broad claims promoting its efficacy for pain relief. Neither one of your ads presents in the body of the advertisements any information from the boxed warning discussing OxyContin's potential for abuse and the related considerations when prescribing the drug. Neither one of your ads presents in the body of the advertisements any information from the boxed warning disclosing that the drug can be fatal if

taken by certain patients or under certain conditions. It is particularly disturbing that your November Ad would tout "Life With Relief," yet fail to warn that patients can die from taking OxyContin.

These ad presentations are accompanied by a brief summary of the prescribing information for OxyContin, including the boxed warning, and the ads include a reference to the brief summary. However, presenting important risk information in this manner is not in accordance with FDA's prescription drug advertising regulations. See 21 CFR 202.1 (e)(3)(i) (Untrue or misleading information in any part of the advertisement will not be corrected by the inclusion in another distinct part of the advertisement of a brief statement containing true information relating to side effects, contraindications, and effectiveness of the drug.) The typical physician reviewing an advertisement for a prescription drug would expect the most serious risks associated with the drug to be included in the body of the ad. The body of these ads contains no discussion of the potentially fatal risks associated with the drug and its potential for abuse. Moreover, the expectation that the most relevant risks have been disclosed in the body, rather than the brief summary, of your ads is exacerbated by having a statement in the body of your ads that begins "The most serious risk.. ." implying that what follows is a complete statement of the drug's most serious risks, not that there are other, m serious risks to be aware of. Therefore, the language in the body of your ads reinforces the impression that the most serious risks have been disclosed, when in fact they have not.

Minimization of risk in information presented

Your ads not only omit these important risks, but also understate the minimal safety information that you do disclose in the body of the advertisements, thus completely misrepresenting the safety profile of the drug. Your ads state that "The most serious risk with opioids, including OxyContin®, is respiratory depression." This statement suggests that there are no specific safety considerations for OxyContin related to respiratory depression, which is false or misleading and could lead to prescribing of the product based on inadequate consideration of risk. This statement also fails to warn that this risk can be a fatal one. As stated in the boxed warning, OxyContin has two tablet strengths that are for use in opioid-tolerant patients only, because they can cause fatal respiratory depression when administered to patients not previously exposed to opioids. Also, the boxed warning states that OxyContin tablets are to be swallowed whole and not broken, crushed or chewed, because that leads to rapid release and absorption of a potentially fatal dose of OxyContin. It is especially troubling that your ads tout the dosing convenience of OxyContin as a benefit, but fail to warn of these associated serious safety risks that come from its controlled-release formulation.

Your advertisements, in this context, also minimize the most common adverse events associated with OxyContin by describing "Common opioid side effects" rather than side effects and safety risks that have been seen with OxyContin itself. In addition, your advertisements state that "OxyContin is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated," without giving the specific contraindications noted above. By essentially suggesting that no safety or tolerability issues have been seen specifically with OxyContin, and by implying that OxyContin therapy is not associated with the serious and significant risks outlined above, your advertisements grossly misrepresent the safety profile of

OxyContin. This implication is false or misleading and raises significant public health and safety concerns.

Overbroadening of Indication

Your advertisements suggest that OxyContin can be used in a much broader range of pain patients than has been proven to be safe and effective. This is even more problematic from a public health perspective given the serious safety risks associated with the drug and the serious deficiencies in the safety information presented in your advertisements.

The only indication information presented in the body of the advertisements (indeed, the only information from the boxed warning included at all as part of the body of these advertisements) is the partial language from the Indications and Usage section of the PI, "For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time," which you present by itself at the top of these advertisements. In the November Ad, this information is located in the upper left-hand comer of the picture on the first page of the spread, in small white type over a background of green leaves and blue sky. It is also the only writing on that page. This information is not prominent, and is not adequately communicated, especially in contrast to the prominent claim of "THERE CAN BE LIFE WITH RELIEF" and all the other text of the advertisement on the next page. Similarly, in the October Ad, this partial indication language is included at the top of the ad in a much smaller typesize than the prominent claims related to "effective relief' with the drug. These presentations are insufficient to give appropriate context and balance to your claims broadly promoting the use of this drug for pain relief. In addition, in your November Ad, you portray a seemingly healthy, unimpaired man out fishing and taking care of a child, rather than depicting a more typical person with persistent, moderate to severe pain taking OxyContin. Therefore your advertisements fail to adequately communicate the actual indication for OxyContin and suggest its use for pain relief in a much broader range of patients than indicated.

In addition, your advertisements fail to present in the body of the advertisements the other important limitations on the indicated use of OxyContin as noted above. Although you prominently claim effective "relief' and that the product "works," you fail to qualify that, as per the boxed warning, OxyContin is not intended to be used as a prn (as needed) analgesic. In fact, your October Ad prominently directs physicians to prescribe OxyContin "WHEN IT'S TIME TO CONSIDER Q4-6H OPIOIDS," which could easily suggest pm use. (Q4-6H indicates 4-6 hours of effectiveness.)

Also of concern, your advertisements, and in particular, your October Ad, represent the dosing convenience of OxyContin by showing dosage cups of the type used to dispense medication in a hospital setting, along with your broad claims of efficacy. The body of the advertisements, however, fails to present the important limitations on the use of OxyContin restricting it to certain hospitalized patients, as described in the OxyContin PI. Most notably, the PI states that OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established. OxyContin is also not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time. The PI also states that

OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain). You fail to present in the body of your advertisements any of these important limitations, thus suggesting the use of OxyContin in inappropriate patients

Conclusions and Requested Actions

You have disseminated promotional journal advertisements that fail to disclose in the body of the advertisements serious and significant risks associated with the use of OxyContin and important limitations on the indicated use of the drug.

Because of the significant public health and safety concerns raised by your advertisements, we request that you provide a detailed response to the issues raised in this Warning Letter. This response should contain an action plan that includes:

1. Immediately ceasing the dissemination of these advertisements and all other promotional materials that contain the same or similar violations outlined in this letter.
2. Providing a plan of action to disseminate accurate and complete information to the audience(s) that received the misleading messages
3. A written statement of your intent to comply with "1" and "2" above.

Please respond in writing to DDMAC by January 24, 2003 of your intent to comply with DDMAC's request. If you have any questions or comments, please contact Mark Askine or Carol Barstow by facsimile at 301-594-6759 or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for OxyContin, and may determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #11400 in addition to the ANDA number.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,
(See appended electronic signature page]
Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing, Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Thomas Abrams
1/17/03 04:31:31 PM

JAMA advertisement-October 2002
JAMA advertisement (Label Summary)-October 2002
JAMA advertisement (Label Summary)-October 2002
JAMA advertisement-(Label Summary)-November 2002
